UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ASHLEY I. BUSH, XUDONG HUANG, CRAIG S. ATWOOD, and RUDOLPH E. TANZI

Appeal No. 2005-0764
Application No. 09/380,704

HEARD: May 5, 2005

Before ELLIS, SCHEINER and MILLS, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1-2 and 37. Claim 38 is also pending and has been objected to as dependent upon a rejected base claim. Final Rejection, page 4.

Claim 1 is illustrative of the claims on appeal and reads as follows:

> 1. A method of treating amyloidosis in a subject, said method comprising administering to said subject an effective amount of (a) bathocuproine or a hydrophobic derivative thereof; and (b) one or more pharmaceutically acceptable carriers or diluents; for a time and under conditions to bring about said treatment; and

wherein said bathocuproine or hydrophobic derivative thereof reduces, inhibits or otherwise interferes with amyloid beta peptide (Aβ)-mediated production of radical oxygen species.

The prior art references relied upon by the examiner are:

Crapper-McLachlan et al. (Crapper), "Intramuscular desferrioxamin in patients with Alzheimer's disease, Lancet, Vol. 337, No. 8753, pp. 1304-1308 (1991)

Cuajungco et al. (Cuajunco), "Metal chelation as a potential therapy for Alzheimer's disease, Annals NY Acad. Sci., Vol. 920, pp. 292-304 (2000)

Halliday et al (Halliday), "Alzheimer's disease and inflammation: A review of cellular and therapeutic mechanisms," Clin. Exp. Pharmacol. Physiol., Vol. 27, pp. 1-8 (2000)

Cherny et al. (Cherny), "Treatment with a copper-zinc chelator markedly and rapidly inhibits β amyloid accumulation in Alzheimer's disease transgenic mice," Neuron, Vol. 30, No. 3, pp. 665-676 (2001)

Fonte et al. (Fonte), "The severity of cortical Alzheimer's type changes is positively correlated with increased amyloid-β Levels: Resolubilization of amyloid-β with transition metal ion chelators," J. Alzheimer's Dis., Vol. 3, No. 2, pp. 209-219 (2001)

Gillmore et al. (Gilmore), "Amyloidosis: A review of recent diagnostic and therapeutic developments," Br. J. Haematol., Vol. 99, pp. 245-256 (1997)

Gnjec et al. (Gnjec), "Transition metal chelator therapy-a potential treatment for Alzheimer's disease?," Frontiers in Bioscience, Vol. 7, pp. d1016-1023 (2002)

Ritchie et al. (Ritchie), "Metal complexation with iodochlorhydroxyquin (clioquinol) targeting Aβ amyloid deposition and toxicity in Alzheimer's disease: proof-of-concept and safety.," Draft Manuscript, January 30, 1993 (eventually published in Archives of Neurology, Vol. 60, pp. 1685-1691 (Dec. 2003).

Grounds of Rejection

Claims 1-2 and 37 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.

We reverse this rejection.

DISCUSSION

35 U.S.C. § 112, first paragraph

Claims 1-2 and 37 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988), delineated the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation which include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Our reviewing court has addressed the issue of relying upon in vitro data to establish a practical utility under § 101 of the statute in Fujikawa v. Wattanasin, 93 F.3d 1559, 1964-1965, 39 USPQ2d 1895, 1899-1900 (Fed. Cir. 1996). There the court considered and discussed the previous case of Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), stating:

> There, we expressly held that, in appropriate circumstances, evidence of in vitro testing could adequately establish a practical utility. As we there explained:
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> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. . . . [U]nder the circumstances of the instant case, where [an application] discloses an in vitro utility, . . . and where the disclosed in vitro utility is supplemented by the similar in vitro and in vivo pharmacological activity of structurally similar compounds, . . . we agree with the Board that this in vitro utility is sufficient to [establish utility].

Id. at 1051, 224 USPQ at 748. Thus, Cross holds that positive in vitro results, in combination with a known correlation between such in vitro results and in vivo activity, may be sufficient to establish practical utility. We will consider the examiner's conclusion that the specification fails to enable the claimed invention with this precedent in mind.

According to the Examiner, "the specification only outlines a prophetic procedure (not a working example) for a method of treating amyloidosis in a subject by administration of bathocuproine and a pharmaceutically acceptable carrier... This is not adequate guidance, but is merely an invitation to the artisan to use the current invention

as a starting point for further experimentation. The claimed method may not necessarily treat amyloidosis in vivo." Answer, page 5. The examiner continues, "there is little guidance in the specification at pg 45-49 regarding specific dosages, duration of treatment, or route of administration for bathocuproine or how to overcome obstacles encountered in prior art disclosures of administration of metal chelators or treating amyloidosis, generally." Answer, page 5. The examiner cites Gillmore, Fonte, Cuajungco and Gnjec to support the position of lack of enablement.

In response, the appellants first argue that the "examiner has not put forth any evidence to support the assertions that determining (a) the optimal quantity of bathocuproine to be administered, (b) the duration of treatment, and/or (c) route of administration would have required 'trial and error experimentation.'" Brief, page 11.

We are not persuaded by the examiner's argument that Gillmore, Fonte, Cuajungco and Gnjec support lack of enablement for failure to recite proper dosages, etc. For example, the examiner argues that Fonte suggests that the administration of metal chelators to subjects causes high toxicity and severe physiological side effects, and that Gillmore states that few clinical trials have been performed relating to amyloidosis. These arguments do not address whether the specification describes proper dosage amounts.

As explained in In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995), the USPTO should not confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a

particular drug for human consumption," citing Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). It is not within the purview of the USPTO to review issues of safety. Nor are safety issues relevant to the claims before us. Fonte suggests that the metal chelators are able to resolubilize Aβ and promote the increased clearance of soluble Aβ. Page 217. The examiner does not specifically indicate where each of these references provides reasons why one of ordinary skill in the art would not have been able to determine appropriate dosage amounts, etc. to practice the claimed invention within the scope of the claims, especially in view of the results of the in vitro model used by Appellants.

We agree with appellants, that with respect to the issue of dosage, duration of treatment and mode of administration of bathocuproine, we do not find that the examiner has put forth a prima facie case of lack of enablement supported by appropriate evidence. Appellants argue the specification provides guidance with respect to the frequency with which chelators may be administered, specification, page 45 and provides administration guidelines for the treatment of mildly, moderately and severely affected patients suffering from amyloidosis, specification, page 45. Brief, page 8. Details regarding the routes of administration are provided for in the specification pages 46-49. Id. We do not find the examiner has provided evidence to support the position that one of ordinary skill in the art would find this information insufficient to practice the claimed method.

The examiner also discusses several of the Wands factors, including the level of unpredictability in the art, the breadth of the claims, and lack of working examples to support his prima facie case of lack of enablement. Answer, pages 6-7. It would appear that the examiner, however, failed to appreciate the state of the art and the in vitro data when making such Wands factor determinations.[1]

In addition, the examiner argues "the in vitro Aβ solubilization results obtained with a metal chelator, bathocuproine, may not necessarily be indicative of the results obtained with bathocuproine in vivo..." Answer, page 7. Appellants also argue that "no evidence has been presented to support the assertion that the in vitro results with bathocuproine are not indicative of the biological results that would be obtained when bathocuproine is administered to a subject." Brief, page 21. For these reasons, appellants argue that the examiner has improperly shifted the burden to appellants to show enablement, when the law requires the examiner to carry the burden, in the first instance, and to provide evidence to support the position of lack of enablement of the claims. Id.

Countering the argument of the examiner, appellants also argue that the in vitro solubilization of Aβ from brain homogenates model is recognized in the art as being predictive of the in vivo results of metal chelators. Reply Brief, page 4. In support of this argument, appellants state that both Cherny and Richie (of record), evince that

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[1] See discussion below regarding the general action of metal chelators in solubilizing Aβ deposits, and its recognized link to amyloidosis.

clioquinol, a metal chelator, was found effective to treat Alzheimer's disease, and "was originally found to promote the solubilization of Aβ from brain homogenates." Reply Brief, page 5.

The examiner responded, arguing that "[c]lioquinol ... is specific for copper and zinc ions and has a different chemical make-up and structure than bathocuprione [sic] ..., which is specific for copper." Answer, page 30. Appellants counter, arguing that "the Examiner has not explained why such differences at the chemical level make it unlikely that bathocuproine would exert therapeutic effects when administered to a subject." Brief, page 23.

In our view, appellants have shown with sufficient evidence (Cherny and Richie) that the in vitro testing of metal chelators involving solubilization of Aβ from brain homogenates is an art accepted model which is predictive of in vivo results. While we recognize, as does the examiner, that possibly better transgenic animal models of Alzheimer's disease may have been available in the art at the time the application was filed, the patent law does not require that the best model be used, only that the model be accepted in the art as predictive of in vivo activity. Cf., Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985).

Finally, we address the examiner's argument that other known metal chelators, such as clioquinol, have a different chemical make-up and structure than bathocuproine, and thus bathocuproine may have different, unpredictable physiological effects after administration to a subject than does clioquinol. Answer, page 30.

As discussed in the specification, and as confirmed in the prior art of record, those of ordinary skill in the art, and the state of the art, recognize some association between amyloidosis and polymers of Aβ which are neurotoxic to neurons in culture. Aβ-mediated neurotoxicity may be the result of the production of reactive oxygen species (ROS) such as hydroxyl radical, superoxide anion, and hydrogen peroxide. Brief, page 3; see also, specification, pages 1-4. Since Aβ deposits are believed to be the cause of the tissue toxicity associated with amyloidosis, agents that interfere with or reverse Aβ deposition are sought to treat amyloidosis. Id. The regulation of copper and zinc is known to be abnormal in the brains of Alzheimer's disease patients, and it has been found that zinc and copper are integral components of Aβ deposits. Id.

Gnjec states that "transition metal ion binding was shown to modulate Aβ solubility as well as its hydrogen peroxide production" and that in vitro and in vivo studies into the effects of transition metal chelator treatments on Aβ solubilization and neuronal function have been published and have yielded promising results. Abstract. Cherny found that treatment with copper-zinc metal chelator markedly and rapidly inhibits β-amyloid accumulation in Alzheimer's disease transgenic mice. See abstract. Cuajungco also noted that metal chelators, generally, and particularly those specific for copper and zinc, are useful for the resolubilization of assembled Aβ. Page 295.

It would reasonably appear that the prior art of record would be understood by those of ordinary skill in the art to support a causal link between amyloidosis and Aβ deposits and that metal chelators of copper and zinc of varying chemical structure are reasonably effective in resolubilizing Aβ deposits. In view of the above, we do not find the examiner has put forth sufficient evidence to show that bathocuproine does not chelate copper or zinc in a manner similar to that of the metal chelators of the prior art, especially in view of appellants' in vitro data from an art accepted model. We do not find that the examiner has put forth sufficient evidence showing that in view of bathocuproine's differing structure one of ordinary skill in the art would not understand that it would function as a metal chelator, especially in view of the specification, page 93, Table 1, which shows bathocuproine is specific for copper and zinc metals, and the specification, page 117, indicating that "[a]ll chelators significantly reduced the amount of $A\beta_{1-40}$..."

The rejection of the claims for lack of enablement is reversed.

CONCLUSION

The rejection of claims 1-2 and 37 under 35 U.S.C. 112, first paragraph for lack of enablement is reversed.

REVERSED

JOAN ELLIS
Administrative Patent Judge)

TONI R. SCHEINER
Administrative Patent Judge) BOARD OF PATENT APPEALS AND INTERFERENCES

DEMETRA J. MILLS
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